Dissertation on

A STUDY ON SIGNIFICANCE OF HIGH SENSITIVITY C-REACIVE PROTEIN IN PATIENTS WITH METABOLIC SYNDROME

Submitted for M.D. DEGREE EXAMINATION

Branch -1

(GENERAL MEDICINE)

THANJAVUR MEDICAL COLLEGE, THANJAVUR

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

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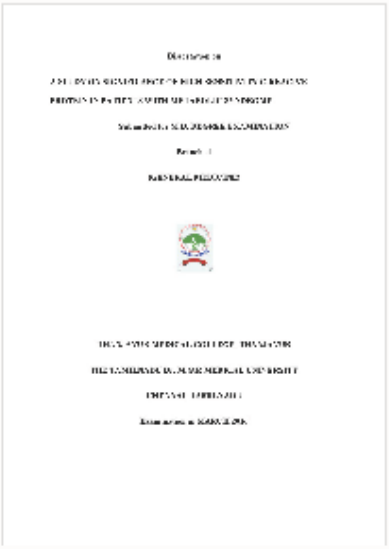

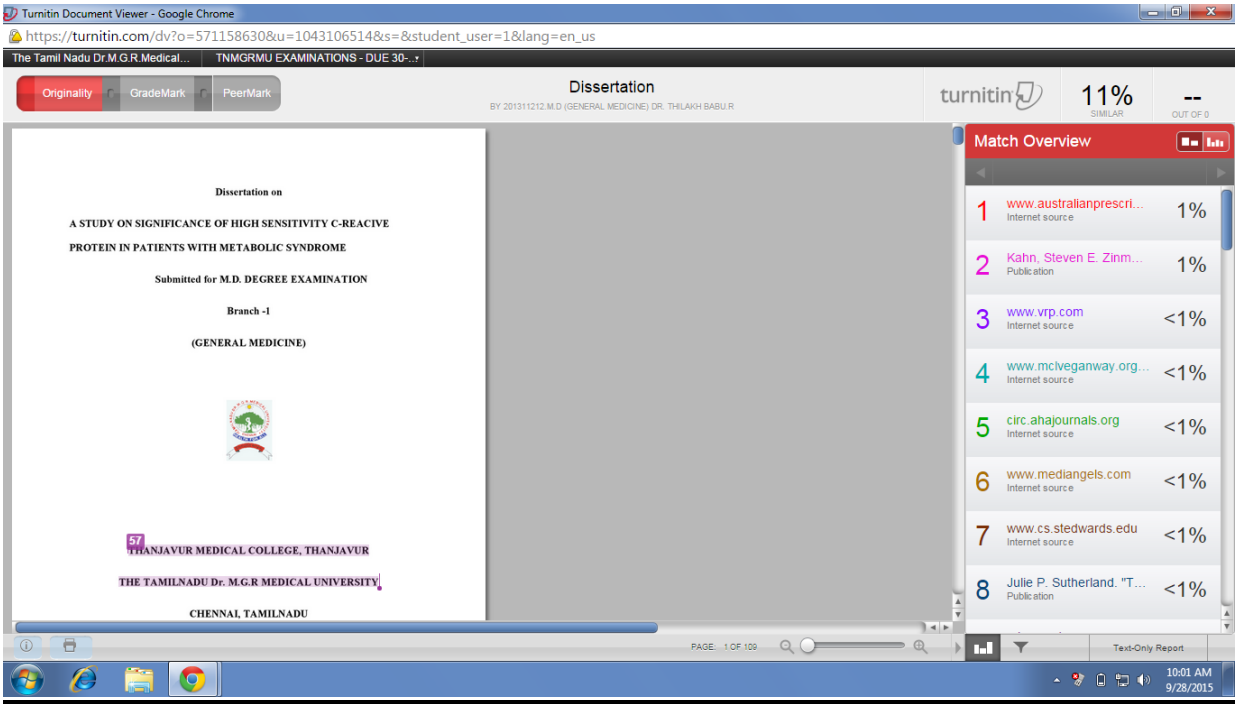
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CERTIFICATE

This is to certify that dissertation entitled STUDY ON SIGNIFICANCE OF HIGH SENSITIVE C-REACTIVE PROTEIN IN PATIENTS WITH METABOLIC SYNDROME is the bonafide record of work done by **DR. THILAKH BABU** in the Department of General Medicine , Thanjavur Medical College, Thanjavur during his Post Graduate Course from 2013 – 2016 . This is submitted as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in April 2016

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DECLARATION

I , **Dr. THILAKH BABU.R** , solemnly declare that dissertation titled **STUDY ON SIGNIFICANCE OF HIGH SENSITIVE C-REACTIVE PROTEIN IN PATIENTS WITH METABOLIC SYNDROME** is a bonafide work done by me at Thanjavur Medical College Hospital during July 2014 – June 2015 under the guidance and supervision of Prof. Dr. K. Nagarajan M.D .HOD., Department of Internal Medicine.

The dissertation is submitted to **THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, TAMILNADU** as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in March 2016.

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DR. THILAKH BABU.R

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CONTENTS

A STUDY ON SIGNIFICANCE OF HIGH SENSITIVE C-REACTIVE PROTEIN IN METABOLIC SYNDROME

Background: Metabolic syndrome is an important risk factor predisposing to Coronary

Artery Disease. HS-CRP, which is an inflammatory marker elevated in cases of Metabolic syndrome.

Methods: We conducted a cross-sectional study signifying the relationship between high-sensitivity C-reactive protein (hs-CRP) with various components of metabolic syndrome in 50 patients with metabolic syndrome at our tertiary care centre in Tamilnadu.

Results: CRP was significantly elevated in cases of Metabolic syndrome. On individual analysis hs-CRP was significantly elevated in women, in patients with Increased waist circumference and impaired glucose tolerance. There was no significant association between hs-CRP level and hypertensive status, Triglyceride levels and HDL levels.

Conclusion: hs-CRP can be used as a surrogate marker of chronic inflammation in patients with metabolic syndrome

Keywords: hs-CRP, metabolic syndrome.

INTRODUCTION

The Metabolic syndrome (MS), also known as syndrome X or Metabolic Syndrome of Obesity is a combination of metabolic abnormalities which confers increased risk of cardiovascular disease (CVD) and Diabetes mellitus.

Pro-inflammatory state due to activation of macrophages and release of Cytokines by expanded adipocytes plays an important role in pathogenesis of this syndrome. This pro-inflammatory state can be documented by estimating the level C-Reactive Protein in serum.

Initially WHO proposed the criteria for defining Metabolic Syndrome in 1988, which has now been evolved through these years; now currently accepted criteria for Metabolic Syndrome is based on the proposed definition given by National Cholesterol Education Programme: Adult Treatment Panel-III (NCEP:ATP-III) which simply is a constellation of multiple clinical and laboratory parameters.

Diabetic Federation de Internationale also came with a new set of criteria defining Metabolic Syndrome, which is also practically in use in certain parts of world. Mainly European Diabetes Society is following the criteria proposed by

IDF. Incidence and prevalence of this syndrome is variable depending on the criteria used for diagnosis.

Since the concept of inflammation gaining momentum we decided to evaluate the levels of high sensitivity CRP in metabolic syndrome. Out of all features of metabolic syndrome, obesity and HDL level were taken into particular consideration. Levels of high sensitivity CRP in obesity patients were analyzed thoroughly. Our study results were compared with existing studies all over the world and India.

AIM OF THE STUDY

AIM OF THE STUDY

1. Analysis of the proportion of patients with Syndrome X having elevated hs-CRP level in serum.
2. To compare the levels of high sensitivity C Reactive Protein (hs-CRP) in obese and non-obese individuals of the study group.
3. To assess whether obesity is a pro inflammatory state.
4. To assess the correlation of high sensitivity C - reactive protein levels with individual parameters of syndrome X.
5. Comparison of our study results with other Indian and foreign study results.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Metabolic syndrome

The combination of multiple risk factors predisposing to atherosclerosis has been named as metabolic syndrome. Names like “metabolic syndrome”, “insulin resistance syndrome”, “syndrome X” signifies a group of conditions present in a patient, which predisposes them to the risk of developing diabetes mellitus, coronary artery disease, cerebral vascular disease and peripheral arterial disease. Other synonyms commonly used are plurimetabloic syndrome, deadly quartet, CHAOS (Australia)[2].

History of metabolic syndrome

In the mid 1920's a researcher named Kylin described a disorder commonly found as a triad of Diabetes Mellitus, Hyperuricemia with associated joint disease and Hypertension as Metabolic Syndrome[3].

Study conducted in l'universite d'Aix-Marseille by researcher Jean Vague[4] during the period of 1940-50 suggested that proportion of distribution of adipose tissue in human body reflects significantly with risk of developing

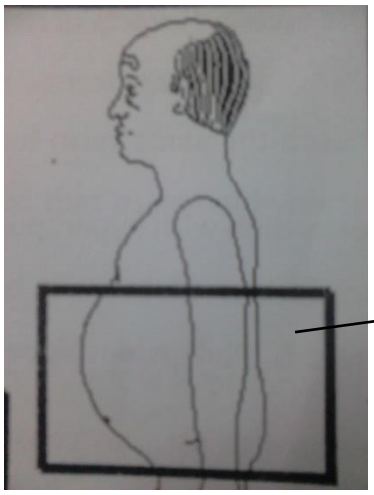
coronary artery diseases, NASH, peripheral vascular diseases, cerebral vascular diseases and hypertension rather than generalized obesity. Based on the observation they classified obesity into two categories.

Android Obesity - also known as central obesity or apple-shaped obesity in which the deposition of fat tissues are seen mainly over central areas of body like waist. It is commonly seen in males.

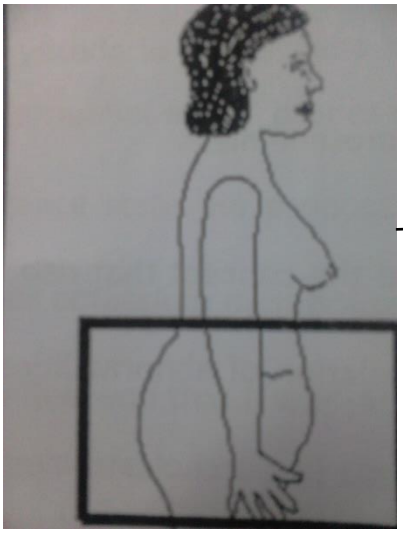
Gynoid Obesity - known as pear-shaped obesity in which deposition of fat in peripheral regions of body like hips, thighs. Such pattern of distribution is seen in females.

They arrived at a conclusion that comorbidities associated with obesity are mostly seen in patients with Android type of obesity, whereas in gynoid obesity such comorbidities are never found. They also found that in patients with Central Android pattern of Obesity, there is a frequent association of type 2 DM, hyperuricemia along with arthritis and renal stones, coronary artery diseases, NASH, peripheral vascular diseases, cerebral vascular diseases and hypertension.

Obesity - phenotypes described by Vague



Android obesity



Gynoid obesity

In mid-1960's study conducted by researcher Avogadro et al[5] in group of six individuals with significant obesity associated with Type 2 DM, dyslipidemia observed that when these persons were monitored strictly with providing reduced energy diet supplemented with diet having reduced proportions of carbohydrates resulted in significant improvement in blood sugar and normalization of lipids.

In 1970's, Haller mentioned that “metabolic syndrome” is associated with Type 2 DM, gout, NASH and dyslipidemia, while studying the comorbid illness found in patients vascular dysfunction[6].

At that period of time another study was simultaneously conducted by researcher Singer[7], described association of hypertension with metabolic syndrome in addition to above mentioned components.

Later in the same decade, Phillips proposed a theory that high risk groups of coronary artery disease usually show combination of comorbid illness which includes Type 2 DM, elevated insulin levels in serum, dyslipidemia like elevated triglycerides, low-density lipids and reduced high-density lipoproteins and hypertension. He also came up with a conclusion that these abnormalities are seen in old age and obesity in addition to myocardial infarction[8,9].

In 1980, researchers from the Goldburg University on Europe analyzed the results of l'universite d'Aix-Marseille conducted by Jean Vague et al and went through their various publications, found that usage of simple bodily measurements provide significant clue in assessing the risk of developing cardiovascular illness, later came up new sensitive parameter for assessing proportion of fat distribution termed it as Waist-Hip ratio[10].

Modan et al observed that elevated insulin level is a common factor found in association with each of the individual components of metabolic syndrome. Increased central obesity and impaired glucose tolerance was significantly related to elevated insulin levels in serum[11].

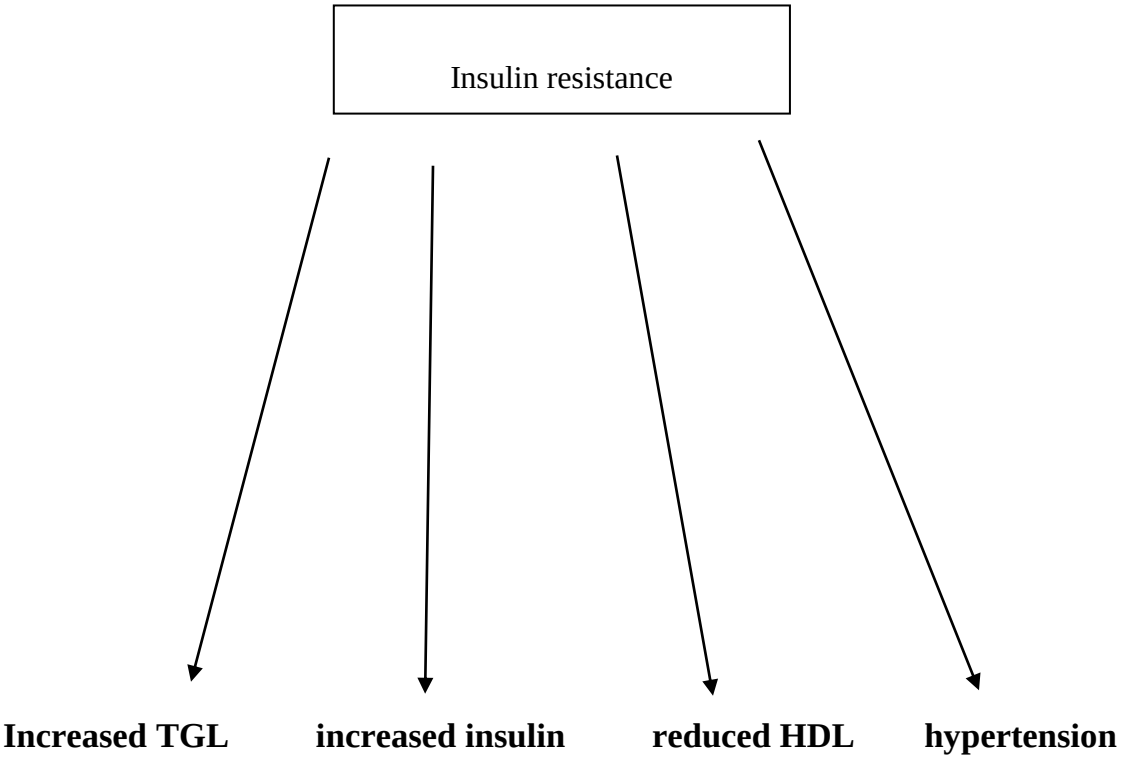
Later some group researchers found simple primary hypertension alone can also be associated with hyperinsulinemia. Increased insulin levels significantly affects carbohydrate metabolism rather than fat or electrolyte metabolism. Such alteration of metabolism along with hyperinsulinemia is seen commonly in muscles, rest of appendicular tissues rather than in liver. Such altered metabolism correlates significantly with hypertension.

In 1988, Banting lecture in the American Diabetes Association coined the term "syndrome X" and suggested that increased peripheral resistance to insulin is the fundamental defect. In that study there is nothing mentioned about

central obesity, whereas it is proved that android obesity is one of the important component of metabolic syndrome[13].

All these studies signified the importance of obesity and insulin resistance as the main etiological factor behind the development of metabolic syndrome.

Syndrome X



Epidemiology

Incidence of metabolic syndrome is variable in various age groups and with ethnicity. It shows a linear correlation with age. It rises from 20 to 50 years and plateaus later off.

NHANES III study[14] observations concluded that nearly 25 percentage of people more than 18 years of age in North America found to be having metabolic syndrome. They fulfilled the individual parameters necessary for developing Metabolic Syndrome.

According to two studies on obesity in India the prevalence of metabolic syndrome ranges from 8% in men to 46% in women[15]. Both these studies used population based samples within the age range. Yet there was significant difference in the prevalence of metabolic syndrome, ranging from 13% in Jaipur[16] to 41% in Chennai[17].

Another study conducted in Chennai[18] observed that the incidence of Metabolic Syndrome was around 12% which correlates with results of study conducted in Rajasthan. This study make use of European Criteria published in 1999, known as European Group for the study of Insulin Resistance Syndrome

criteria. Hence it shows that though people belong to same race or community there appears to be significant variations in incidence of syndrome X and its various components of the syndrome separately when measured alone.

In late 1990's World Health Organization came up with common definition for this disorder applicable to all group of people living in various regions of the world and coined the term Metabolic Syndrome. Currently accepted and followed criteria is proposed by National Cholesterol Education Program (NCEP) - Adult Treatment Panel (ATP III.

WHO

WHO criteria[19]:

Essential components

Type 2 Diabetes Mellitus

Impaired glucose tolerance,

Impaired fasting glucose or insulin resistance

AND two of the following:

Systolic BP > 140 or Diastolic BP>90 mm Hg

Altered fat metabolism

Serum TGL ≥ 150 mg/dL

Serum HDL

≤ 35 mg/dL in men

≤ 39 mg/dL in women

Obesity

WHR > 0.90 in men

> 0.85 in women

Or

Quatelet index > 30kg/m2

Micro albuminuria - urinary albumin excretion ratio ≥ 20mg/min

Or albumin: creatinine ratio ≥ 30mg /g

- **European Group for study of Insulin resistance definition for Metabolic Syndrome (EGIR 1999)[19]**

  - Proposed criteria mainly give importance to Insulin resistance, hence it is also called as Glucocentric criteria

  Components are:

1. Peripheral resistance to Insulin or elevated insulin level in serum

   (Plasma insulin more than 75th percentile).

Any two of the below

1. Obesity: Waist circumference

   > 102cm (men)

   > 88cm (women)

2. Lipid derangement:

   Sr. TGL > 2 mmol/L or

   Sr.HDLC <1 mmol/L

3. Hypertension

   Systolic BP $\geq$ 140 or

   Diastolic BP $\geq$ 90 mmHg

4. Fasting Blood sugar $\geq$ 110 mg/dl

The US National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following[20]

1. Blood pressure — Systolic > 130 or Diastolic BP > 85 mm Hg or on anti-hypertensive drugs
2. Fasting blood sugar — $\geq$ 110mg/dL or on oral hypoglycemics or known case of Type 2 DM
3. Plasma triglyceride — $\geq$ 150mg/dL or specific medication
4. Plasma HDL
   - Male $\leq$ 40mg/dL or specific medication
   - Female $\leq$ 50mg/dL
6. Waist circumference
   - Male $\geq$ 102cm
   - Female $\geq$ 88cm

Presence of three or more of the above risk factors constitute metabolic syndrome.

Modified NCEP 2004 changed the existing cutoff level of fasting plasma glucose to $\geq$ 100mg/dL.

American Heart Association / NHLBI (2005)[21]

1. central obesity

- Males – ≥ 102cm
- Females – ≥ 88cm

2. Increased TGL: ≥ 150 mg/dL

3. Low HDL-C:

Males – < 40 mg/dL

Females – < 50mg/dL

4. Hypertension:

Systolic BP > 130 or Diastolic BP > 85 mm Hg or when the patient is on antihypertensive.

5. Impaired glucose tolerance:

Fasting blood sugar > 100mg% or when the patient is hypoglycemic agents.

IDF Criteria for abdominal obesity[22]

IDF came up with new set of criteria which is in use in European countries and some Diabetic associations in Europe

International diabetic federation has proposed the following recommendations for central obesity.

Waist Circumference			
Men	Women	Ethnicity	
>94cm	≥80cm	Europid, Sub-Saharan African, Eastern & Middle Eastern	
≥90cm	≥ 80cm	South Asian, Chinese and ethnic South & Central American	
≥85cm	≥ 90cm	Japanese	
Two or more the following			

Fasting triglycerides > 150 mg/dL or specific medication
HDL cholesterol <40mg/dL and <50mg /dL for men and women, respectively, or specific medication
Blood pressure > 130 systolic or > 85 mm diastolic or previous diagnoses or specific medication
Fasting plasma glucose > 100mg/dL or previously diagnosed type 2 diabetes

Etiology of metabolic syndrome is not clearly understood. Basic pathogenesis of this syndrome is very confusing.

Important risk factors are:

1. Old age
2. Hereditary and
3. Sedentary habits

Still there is a controversy existing between researches regarding the etiology of metabolic syndrome .Some group proposes insulin resistance as the basic defect for development of metabolic syndrome. Other group strongly suggests obesity as the underlying etiology in development of metabolic syndrome. Very few authors says that both the obesity and insulin resistance are due to rather advanced systemic abnormalities.

Almost all the study results showed that when insulin resistance is absent then the persons will not show features of metabolic syndrome, but not all the patients with syndrome X will be having obesity.

Pro-inflammatory cytokines are found to be elevated in patients with metabolic syndrome. Common observed ones are interleukin 1, 6 and 18; C - reactive protein; TNF-alpha, resistin;

Pathophysiology

Abdominal adipocytes secretes numerous fatty acids, angiotensin-II and adipokines into circulation[25]. The increase in free fatty acids[26] reduces the uptake of glucose by muscle[27]. Excess free fatty acids and angiotensin II are harmful to pancreas and causes destruction of acini[28]. Although pancreas manufactures excess insulin, it is just not enough to counter fasting hyperglycemia. This explains the paradox of fasting hyperglycemia in spite of increased plasma insulin levels in insulin resistance syndrome. Changes associated with metabolic syndrome are,

1. Lipoprotein – increase in apo B, Lp (a)

2. Prothrombotic state – increase in fibrinogen, Plasminogen activator inhibitor 1
3. Inflammatory markers – increase in CRP, TNF, IL 6
4. Vascular – micro albuminuria
5. Increase in serum uric acid, homocysteine
6. Nonalcoholic fatty liver disease
7. Obstructive sleep apnea
8. Polycystic ovaries

Obesity – Is it a disease???

The current developments in health sciences look at obesity as a starting point of all disease process.

According to WHO the global burden of obesity and overweight is projected as follows.

In 2005:

Nearly around 16,000 million persons above 15 years of age were having BMI > 25;

Around 4 billion were found to have obesity.

In 2015:

Over 19,000 million persons over 18 years were having BMI > 25;

Among them over 6 million were obese.

40% of persons over 18 yrs of age have BMI > 25 and 13% were

Having BMI > 30.

Most of the world's population live in countries where overweight and

Obesity kills more people than underweight.

42 million children under the age of 5 were overweight or obese in 2013.

Obesity is preventable.

At least 20 million children under the age of 5 years are overweight globally in 2005.

Initially thought to be a disease of developed countries, now incidence and prevalence of obesity and insulin resistance were showing increasing trends

in developing and under-developed countries mainly because adopting western lifestyles.

Energy consumption and energy expenditure are important determinants in developing obesity. When there is disparity in consumption of calories and amount of calories spent by the patient by routine daily activities predisposes to the development of obesity.

Rising trends in prevalence of obesity is due to,

Global shift in diet towards increased intake of energy – dense foods that are high in fat and sugars but low in vitamins, minerals and other micronutrients; and

A trend towards decreased physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.

Height, weight and Waist circumference are the key determinants in estimating obesity. Most important index used to define Obesity is body mass index (BMI), also known as the Quetelet index. Body Mass Index nearly reflects the amount of body fat in many persons, which is measured as

Weight in Kg/Height square in meters.

The Deurenberg equation is used to estimate the body fat percentage as follows: body fat percentage = 1.2 (BMI) (+ 0.23 (age) – 10.8 (sex) – 5.4, where age is in years and sex is 0 for female and 1 for male.

The international Classification of adult underweight, overweight and obesity according to BMI (adapted from WHO 2005).

But there is a slight change in this proposed criteria which is in use in India. Based on which classification of obesity is defined. Below mentioned classification is the international standard criteria.

World Health Organization proposed a strategy on Lifestyle modifications like Food habits, exercise and health, which promotes practices which need to be followed in order to obtain good quality of food and carry out routine exercise.

The proposal encourages all medical and paramedical staffs to carry out all necessary measures at international, national and community level in order to decrease incidence of non-communicable diseases and also to give significant importance to primary prevention strategies for eliminating the modifiable factors responsible for those diseases.

	BMI(kg/m²)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 22.99
		23.00 - 24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	≥30.00	≥30.00
Obese class I	30.00 - 34.99	30.00 - 32.49
		32.50 - 34.99
Obese class II	35.00 - 39.99	35.00 - 37.49
		37.50 - 39.99
Obese class III	≥40.00	≥40.00

WHO CRITERIA FOR OBESITY

Proposed strategy by World Health Organization is a component of their Chronic Disuse Control guidelines under the separate area of health network for non-communicable disease prevention under the control of WHO

Goals of this strategy are:

i. Educate all people about non-communicable disease control measures;
ii. Adequate importance must be given for people below the poverty line
iii. Controlling the modifiable risk factors thereby retarding the progression of chronic diseases;
iv. Reducing the mortality and morbidity associated with chronic diseases.

Major health sectors are also supporting this project by framing the refined objectives accordingly, which is based on regional requirements.

They are mainly focusing on people who are more prone for developing these non-communicable diseases and educating them to take properly and adequately nourished food, recommending exercise schedule based on their preferences through promotional campaigns, posters, advertisements in the media and routine health camps.

They also help underdeveloped nations by financial assistance in order to frame and implement programmes necessary to achieve the strategic goals in addressing the issues related to diet and health. Majority of such programmes

being conducted in African and Asian countries under various levels, still the prevalence of chronic diseases are on rise. But some sectors of health related activities showing good progress, they will be able to reach goals in the near future.

Hence, in the eyes of WHO and various other health groups obesity is a burden on health and a possible disease process. It is now seen as an ongoing inflammatory process which, like diabetes, leads to increase in the cardiovascular morbidity and mortality. Hence, obesity is considered as an important component of metabolic syndrome and as an independent risk factor for cardiovascular disease.

Physical inactivity

Sedentary life habits are important determinants to develop metabolic syndrome. It also predisposes the patients in developing dyslipidaemia, insulin resistance and obesity which are the individual parameters of metabolic syndrome. Increase in physical exercise was one important lifestyle modification in primary and secondary prevention of metabolic syndrome.

Studies shows persons who involve in sedentary activities

like playing video games and spending time in internet have increased risk of developing metabolic syndrome, when compared with those who do physical exercises for more than 30 minutes daily.

Assessing the level of physical activity

Physical activities are assessed in various ways by the type of activity , timing and hours spent on such activities, and also by ecological conditions of the place where they carry out such activities. Other than physical exercise, energy expenditure is also based on the Occupation, whether it is associated with workload, continuous strain or Intermittent strain and the person's choice of recreation, mode of recreation.

Various methods in which quantification of physical activity can be done are

- Indirect calorimetric method
- Accelerometer method using sensors
- Physical activity associated heart rate variation assessment
- Self-reporting estimation method

Type of method of assessing the physical activity is individualised according to targets, study group size, financial resources, social factors and also reliability of the methods.

Accurate modes of measuring amount of energy expenditure

are water labelling method and calorimetric method. But they are not practically useful for measuring a large group of population, hence in such conditions self-reporting method is used, though they are not as sensitive and specific as instrument dependant methods.

Indirect calorimetric method

Most sensitive and precise method of assessing energy expenditure and calories spent during rest and with rest.

Two steps in the assessment of energy spent using indirect calorimetric method are

First the expired air is collected in closed container like airtight Container or plastic bag.

Second, the open system in which measurement of amount of energy Spent are quantified over prolonged period.

Depending upon the person's respiratory activity, the energy spent are assessed by the formula

REE = [VO2 (3.94) + VCO2 (1.11)] 1440 min/day

Where

REE = resting energy expenditure,

VO2=oxygen consumption &

VCO2 =carbon dioxide production.

This formula reflects amount of oxygen consumption and carbon-di-oxide Production is closely related to energy expenditure.

But this method is practically not feasible.

Double-labelled water method:

This method utilizes radio-labelled isotopes for assessing energy expenditure. Study group of people were given a dose of heavy water and they will receive normal water of about 15-20 ml.

After a period of fasting of about 8 hours, baseline urine sample was collected for 0-hour isotope measurement.

2^{nd} urine sample will be taken after four hours of giving radio-isotope.

This sample measures total body water.

3^{rd} sample will be taken after 24 hours of isotope administration time.

From then on, at least 2 samples of urine has to be collected from the starting and finishing time of the study in order to estimate the amount of energy spent. Normal period of study is 3 weeks.

The daily food intake is noted during the observation period and the diet remains the same throughout the study for the most accurate results and the respiratory quotient (RQ) calculated based on daily intake. Any body fluids will be useful assessing the space, but preferred specimen is urine

due to methods used for collection are not cumbersome.

Accelerometer:

Accelerometer estimates amount of acceleration gained with fall. The instrument is positioned upper or lower parts of body usually at the Bony prominence. This method is used to differentiate the variation in levels of activity among different persons and estimate the level of changes that can be made by introducing any intruding things.

For type every action carried out, persons will be given specific Basic Score. They are as follows

Sedentary activity - < 800/min

Mild workload – 800-3199/min

Medium workload – 3200 – 8200/min and

Severe workload - > 8201/min

Metabolic equivalent value is assessed by using an equation having parameters like age of the patient and score obtained by them.

Heart rate variation estimation method:

Heart rate variation of the patient while doing physical exertion is Estimated in this method. Usually heart variation is directly proportional to the amount of workload, which in turn gives objective evidence of amount

of energy spent by the patient.

Leads are placed around the thorax which will be having a Bluetooth Communication with wristwatch for monitoring the activity.
Main endpoint is measured as duration of time required to perform an action when the patient is in baseline heart rate or converting the heart rate into baseline level. By this method the amount of energy spent is indirectly measured using specific equation.

Since there are multiple factors which can cause increase in heart rate it may lead to confounding bias resulting inaccurate estimation.

Self-reporting method:

One of the commonly employed ways of assessing physical exertion which are also known as interview-method.

Questions are prepared by using various studies, which assess the individual level of activity with correspondence to their social background are in use. They estimate the amount of energy spent based on available log of questions. Usually it is done retrospectively by asking workload during past one month and roughly estimating the amount of energy spent.

There are multiple ways of assessing the activity. Commonly it is based on the duration in which longer duration recall for example for one month period givers overall idea about type of manoeuvres the people in particular social background are following. Whereas the small duration questioning method is used for epidemiological surveys which gives the photograph of the population under study.

Pathophysiology of obesity

The pathogenesis of obesity is simply not an imbalance between energy intake and energy output, it is far more than that. Although this concept allows easy understanding of the various mechanisms involved in the development of obesity, obesity is simply not the result of too much eating and/or too little exercise.

Two major factors that are variably involved in the development of obesity are genetics and environmental factors. Off springs are at increased risk of obesity when both parents are obese and in monozygotic twins there is increased prevalence of obesity.

Leptin:

Leptin is a protein synthesized and secreted mainly by adipocytes plays an important role in regulation of body weight.

Leptin was discovered by Freidmen in 1990, following which there is increase in wide variety of studies based on leptin was conducted resulting understanding it major role in controlling satiety cycle and food intake. The term leptin suggests “Thin” in Greek.

Initially it was thought that food intake and satiation is controlled by ventromedial nucleus and limbic system of hypothalamus, which was later proved that neurological control of satiety is more advanced and confusing process difficult to understand.

Leptin functions by signaling hypothalamus regarding satiety thereby resulting in decreased food intake, also decrease in storage of body fat thus causing reduction in body weight. It also protects against gaining weight due to action on altering the metabolism of carbohydrates and burning excessive calories. It is found that obesity is mainly due to resistance to action of leptin

not due to its deficiency. Thus most obese individuals are found to have increased serum leptin levels.

Recent studies have found that leptin is a member of the cytokine family with a helical structure. Helical cytokines are a diverse family of proteins without any detectable sequence of homology between its members. All these cytokines are found to have a four helix bundle that exhibits an up-up-down-down folding pattern. Interleukin-2, interleukin-4, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, and grown hormone are the helical cytokines identified.

Leptin binds to its receptor which belongs to family of cytokines. Janus Kinase activates the receptor resulting in transduction of signal.

By acting centrally on the melanocortin receptor 4 (MC 4) Proopiomelanocortin and alpha melanocyte stimulating hormone reduce the dietary intake.

There are several genes encoding Proopiomelanocortin, mutation in any of these genes causes reduced synthesis of alpha – melanocyte – stimulating hormone. Decreased melanin level in such patients causes presence of red hair.

In addition to that they have absent ACTH in blood causing secondary deficiency of adrenals resulting in obesity. Studies suggests that 4-6% of obese individuals who are under age group of 10 found to have these mutations.

More than 10 different loci has been identified and these mutations accounts for major cause of genetic associated obesity.

Leptin activates PC-1 processing enzyme which plays an important role in the conversion of POMC to alpha – MSH. Peroxisome Proliferator Activator Receptor-gamma is responsible for differentiation of fat tissue cells. If mutation is found in this receptor such patients will be invariably associated with obesity.

Various other genetic disorders associated with obesity are Cushing's syndrome, Hypothyroidism, Insulinoma, Craniopharyngioma and other hypothalamic disorders. Cushing due to genetic defect can be differentiated from routine Cushing's syndrome by measuring cortisol levels in blood and urine in basal state and response to CRH, which will be normal in them. Subtle hypothalamic dysfunction is the major cause of obesity which can be confirmed by radiological studies.

Growth hormone level is found to be decreased in patients with obesity probably as a result of compensatory suppression to increased nutrition supply

Central pathway of leptin mechanism of action is signaling of POMC neurons in hypothalamus resulting in synthesis of alpha-MSH which needs to be processed by PC-1 enzyme. Alpha-MSH binds with melaocortin-4 receptors causing reduced appetite. AgRp known as Agouti-related peptide is an antagonist to the same receptor

Obese Mice or ob/ob mice have mutated ob gene, such mice will eat excessively due to deficient signal control by inadequate leptin affecting neurohormonal control of satiety resulting in extreme obesity. This analysis suggested use of Leptin as a treatment option for obese individuals having deficient leptin due to various hereditary diseases causing excessive and abnormal appetite. Such patients also show reduced activity of t-lymphocytes, immunodeficiency, dyslipidemia, impaired fasting glucose tolerance and various other endocrinological defects.

Blood leptin amount vary between day and night, commonly elevated at night. Various cytokines, insulins and Ang-II causes release of leptin from adipose tissue. Increased level suggests expanded adipose tissue mass and vice-versa.

5 genetic defects in pathway of leptin action are found to be associated with obesity. They are mutation in leptin synthesizing gene, receptor mutation, POMC mutation, melanocortin-4 receptor mutation and PC-1 processor mutation.

CRP AN INFLAMMATORY MARKER

CRP – An inflammatory Marker

Inflammation is the mechanism by which human protects itself against various noxious substances. Absence of which causes poor recovery of traumatized tissues and inability to fight against multiple pathogens resulting in further damage to organs.

Any injury to organs results in inflammation which is followed by acute phase response, which is normal physiological phenomenon occurs when there is infection or inflammation. The response is characterized by various components including fever, enhanced permeability of vessel wall and alteration in level of numerous active substances in blood known as acute phase reactants.

Adipocyte derived- macrophages are the important source of pro-inflammatory cytokines. The pro-inflammatory cytokines are increased in number which are interleukin 1, 6 and 18; resistin; TNF-alpha and serum bio-marker C - reactive protein. Elevated cytokine level reflect over-production of expanded adipose tissue mass.

CRP is a biological substance which was known as an acute phase reactant for long. From that it has progressed on to be known as an important. Inflammatory marker.

Table – 1

Acute – phase proteins

	Increased concentration	Decreased concentration
Protease inhibitors	Alpha1 – antitrypsin	
	Antichymotrypsin	
Coagulation proteins	Fibrinogen	
	Prothrombin	
	Factor VIII	
	Plasminogen	
Complement proteins	C1s, C2, C3, C4, C5 Factor B C1 esterase inhibitor	

	Plasminogen	
Transport and storage proteins	Haptoglobin	Transferrin
	Haemopexin	
	Caeruloplasmin	
	Ferritin	
Miscellaneous	C – reactive protein Procalcitonin Serum amyloid protein Fibronectin Alpha1 – acid glycoprotein	Albumin Pre albumin

CRP is one of the important factor in protection from various infection. It got its name from its activity against C antigen in Streptococcus pneumonia. Initially it was thought to be an antibody reacting against the C-antigen. But after various research it is found to be a separate protein reacting with bacterial antigen. Level of CRP will return to normal once the infection subsides. CRP binds with carbohydrate moiety like choline present in the surface of cell surface of various pathogens

Reaction of CRP with C-antigen causes activation of classical complement pathway and opsonization of specific antigenic components for phagocytosis.

CRP is mainly produced and released by hepatocytes after an inflammatory reaction in body. Release of CRP is promoted by various cytokines predominantly by IL-6. Peak level in serum occurs after 6 hours of inflammatory process initiation, which may around thousand-fold. Half-life of CRP is around 10-30 hours, hence once the inflammatory process subsideslevel of CRP will fall rapidly. In normal personslevel of CRP ranges from 0.9 mg/L – 2.05 mg/L, which will never increase above 5mg/L. Elevation of CRP level above 40mg/L is found in case cell necrosis and bacterial infections.

CRP levels are found to be reduced in case of liver failure and renal insufficiency which will adversely impact the results

CRP in clinical setting

Increased CRP level does not signify any particular pathology, usually increased in inflammatory states (>95%), helpful as an indicator of inflammatory state. It provides a supportive evidence in routine workup of a

patient.CRP level assessment is a useful screening tool, which will signify the severity of disease process.

Conditions in which elevated C-Reactive protein level is seen are

Table 2

Bacterial infections	Pyelonephritis
	Pelvic infections
	Meningitis
	Endocarditis
Hypersensitivity Complication of infections	Rheumatic fever Erythema nodosum
Inflammatory disease	Rheumatoid Arthritis Juvenile Chronic Arthritis Ankylosing Spondylitis Psoriatic Arthritis Systemic Vasculitis Polymyalgia Rheumatica Reiter's Disease Crohn's Disease

	Familial Mediterranean Fever
Transplantation	Renal Transplantation
Cancer	Lymphoma
	Sarcoma
Necrosis	Myocardial Infarction TumourEmbolisation Acute Pancreatitis
Trauma	Burns Fractures

Certain conditions are found to have very minimal elevation of CRP though there is an evidence of inflammation. They are

Table 3

Inflammatory disease	Systemic Lupus Erythematosus Systemic Sclerosis Dermatomyositis Ulcerative Colitis Sjogren's Syndrome
Transplantation	Graft Versus Host Disease
Cancer	Leukemia

In these situations CRP levels are near normal, in spite of having evident high grade inflammatory activity. Pathology behind this process is not fully understood.

In certain diseases like RA, CRP levels are helpful in assessing candidate's improvement in clinical status after initiating treatment. Mainly in RA, CRP level correlates significantly with active disease process and also their response to treatment. Other uses of CRP measurement includes very high elevation of the reactant is seen in bacterial infection rather than viral infection, thus providing a supportive evidence of bacterial pathology.

C - reactive protein is more likely to be highly elevated (More than 100mg/dl) in bacterial rather than viral infection, and it is unlikely to see a normal C – reactive protein in the presence of significant bacterial infection.

C - reactive protein levels are usually remain constant even with usage of NSAIDS or changes in body temperature. So they play a supportive role in clinical assessment in combination with fever charts clinically. In certain diseases like SLE still there confusion exists in differentiating disease flare up

or new onset infection. In such situations measuring CRP level is vital in establishing the presence of infection.

Increased C - reactive protein concentration can affect higher mental functions which includes learning and memory. Various studies confirmed the fact that in patients with dementia or other defects in cognition there is significant rise in the concentration of C - reactive protein in serum. Advanced studies were conducted in past years which proposed a theory that early rise in blood level of hsCRP found to be good predictor of dementia in old age females.

A new study investigating CRP in patients with chronic obstructive pulmonary disease (COPD) indicates this inflammatory marker to be elevated in patients with this lung disease. When researchers measured levels of CRP and the proinflammatory cytokines tumor necrosis factor – alpha (TNF – alpha) and interleukin – 6 (IL – 6) in COPD patients they found that CRP was the only inflammatory marker studied that was elevated in subjects with stable COPD. According to the study authors, "**The present study confirms that circulating CRP levels are higher in stable COPD patients and may thus be regarded as a valid biomarker of low-grade systemic inflammation**". 51

High Sensitivity C reactive protein

High-sensitive C - reactive protein – the term indicates the test used to estimate even the minute changes in CRP level over a normal prescribed range. Hence it is a valuable and sensitive indicator of inflammatory state. Routine latex agglutination test CRP measurements are not very sensitive in diagnosing early stages of vascular dysfunction in atherosclerosis.

High sensitive CRP measurement estimate cardiac risk status in a visibly normal individual when used in combination with lipid profile.

Till now 34 case-control studies demonstrated association between hs-CRP and increased risk of atherosclerosis, 9 prospective study result showed hs-CRP level correlates with prognosis of patients in the metabolic syndrome and risk of developing diabetes mellitus.

AHA/CDC define the risk group as follows

1. Low risk <0.1 mg/dL
2. Average risk 0.1 to 0.3mg/dL
3. High risk > 0.3mg/dL

The relationship between hs-CRP and the components of the metabolic syndrome:

Elevation in concentrations of CRP in cases of obesity and also in Persons with metabolic syndrome have been reported in various studies that too in amounts which were considered as very high risk by researchers across the various nations.

C-Reactive protein level not only reflects the inflammatory Activity and also directly proportional to parameters of metabolic Syndrome. There are various researches which were carried out to establish the relationship between C - reactive protein level and multiple components of metabolic syndrome.

A retrospective study on normoglycemic patients conducted by Yudkin and others proposed that each component of obesity is associated with increase in C-reactive protein level.
It also reflects the risk of developing impaired glucose tolerance, Hypertension, dyslipidaemia and other features related to vascular Defects like atherosclerosis. The researchers came out with a conclusion proposing adipocytes are major stimulator of inflammatory activity

which will predisposes them in developing impaired glucose tolerance and atherosclerosis. They also suggested that these activities acts as a bridge between impaired glucose tolerance , atherosclerosis and cardiac and other systemic complications.

A retrospective study conducted in Tunisia proposed the importance of central obesity as an individual important determinant of CRP levels in patients with metabolic syndrome of both sex. Decrease in HDL-C level in metabolic syndrome especially in women associated with significant rise in CRP level.

In an another retrospective study conducted in Israel also came out with with conclusion that in each parameters of metabolic syndrome C-Reactive protein will be elevated, especially in individuals with central obesity showing higher correlation. Through this researchers proposed that important factor in metabolic syndrome that signifies inflammatory activity is waist circumference. They also pointed out that obese individuals who are not having metabolic syndrome are also at high risk of death due to cardiac illness.

A study conducted in Germany which used BMI rather than waist circumference also proposed that C-Reactive protein level is directly proportional and significantly associated with each of the individual parameters

of metabolic syndrome. P-value of this study if found to be <0.0001. They also showed that with rising numbers of parameter of syndrome X, there will be significant rise in serum levels of C-Reactive protein.

Atherosclerosis remains the major cause of death in developed regions of the world. Patients develop clinical features depending on site of lesion of atherosclerosis. When it affects coronary arteries it causes MI and angina, in cranial vessels results in stroke, limb vessels results in peripheral arterial disease, renal vessels causes renal artery stenosis, aorta causes aortic aneurysm, splanchnic vessels cause mesenteric ischemia. Even though C-Reactive protein predicts the risk of atherosclerosis , studies showed it does not promote atherogenesis, which is in contrast to lipoprotein-a and apolipoproteinc3 which promotes atheroma formation.

Increasing evidence **suggests elevated hsCRP predicts risk of coronary artery disease**. Increased levels of these markers correlates with increased inflammatory state. After death post-mortem studies in myocardial infarction patients showed features of inflammation like deposition of chronic inflammatory cells at regions of infarction. These findings shows C - reactive protein estimation correlates with stages of development of atheroma formation.

Recent studies conducted which are based on statins like JUPITER study and PROVE-IT study showed treatment with statins reduced cardiovascular mortality in patients showed reduction both CRP and lipoprotein level, rather than reduction in either one alone. Mechanism by which statins reduce these CRP level is unknown. Adipocytes of viscera secretes inflammatory mediators which promotes CRP synthesis, important region of CRP production in persons with obesity. Increased CRP levels correlates with increased BMI and increased adipocyte thickness in visceral organs. Loss of body weight is associated with reduction in CRP levels.

CRP estimation

Initially latex agglutination method was used in estimating CRP level which has poor sensitivity in estimating minimal rise in C - reactive protein. Hence proposal for usage of CRP as an indicator of inflammatory state was rejected earlier.

The estimation of CRP was earlier done by ELISA. It threw light into a possibility of CRP being more than just an acute phase reactant. It suggested that normal persons have CRP levels for below the normal cut off value and higher values are associated with increased cardiovascular risk.

Later highly sensitive nephelometry and turbidometry commercial kits are being used in the estimation of CRP.

While measuring hs-C-Reactive protein, things which are taken into consideration are exclusion of any inflammatory state, sepsis, tissue injury etc. If present, then the test should be performed only after two weeks of recovery of sepsis. Sensitivity of test increases with two assays which are done with a gap of four week period, risk assessment is done through smaller value. Usage of C - reactive protein estimation for selecting persons for pTCAis under research.

CRP Aids Risk Stratification

Persons with this syndrome are more prone cerebrovascular disease, intervening at starting stage of disease itself carries good prognosis. C – Reactive protein (CRP) is an indicator of low-grade inflammation which estimates the risk of myocardial infarction, cerebro-vascular disease and death due cardiac illness in normal persons with no history of vascular disease, and among individuals with acute or stable coronary disease, CRP predicts recurrent events and death.

In the Study on Health indicators of Women, elevated C-Reactive protein levels are good indicators of the individual parameters of the metabolic syndrome and metabolic syndrome as a whole. In various analyses, if the CRP

level is less than 1mg/L it has significant correlation with risk free benefit related cardiac illness.

Various studies across the the world came with conclusion that in patients fulfilling the criteria for syndrome X will also have carbohydrate metabolism dysfunction which are dependent on insulin. But in reality it is confirmed that all cases obesity are not associated with glucose intolerance and they show discrete clinical features. Study conducted by Reaven et al., showed that hyperinsulinemia and peripheral insulin resistance is found in patients with syndrome X.

Central obesity plays an important role in development of insulin resistance. Amount of visceral adipose tissues correlates significantly with peripheral resistance to insulin when compared to subcutaneous adipose fat mass. Triglycerides are synthesized by reaction between glycerol and fatty acids, which go and get deposited in adipocytes. In condition requiring energy these triglycerides undergo beta-oxidation of fatty acids and releases energy. In individuals with obesity fatty acids are produced in excess which gets deposited in adipose tissue. It leads onto expanded fat mass, commonly in visceral organs providing favorable conditions for developing insulin resistance.

Chronic inflammatory states are associated with increased vascular complications like atheroma and fibro atheroma formation. Such states may also promotes development of peripheral resistance to insulin, which will further aggravates inflammatory burden. Hence measurement of CRP level correlates significantly with patients having syndrome X, high risk grading based on serum level and assessing the response to treatment.

Inflammation, obesity and CRP

Obesity is mostly associated with moderate amount of inflammatory activity certified by presence of elevated hs-CRP and inflammatory mediators released by macrophages. All these changes will lead on vessel wall changes involving endothelium, promoting atherosclerosis. These features can possibly somewhat explain the development coronary artery diseases in patients with increased fat mass.

Pathophysiology underlying the development of vascular damage in obese individuals is not completely understood. Proposed theories are adipose tissue secrete numerous immunologically active substances known as “adipocytokines”, which modulates the inflammatory activity in various tissues. Thus they may cause significant mortality due to cardiac illness.

Various studies showed that factors present in subcutaneous and visceral adipose tissues secrete multiple immunological substances which are responsible for increased risk of mortality related to cardiac illness. These kind of pathological activities are found to be increased in obesity patients. Such immunological substances are called as "adipocytokines", since they are secreted from adipocytes

Adiponectin

Adiponectin is a hormone synthesized and released mainly from adipose tissues. Main functions of this hormone is found to be enhancing insulin sensitivity, promoting oxidation of lipids. It is also found to be vaso-protective. Obese individual have very low level of adiponectin in their circulation. Reason for this reduced level is not known.

There are various ways in which hormone adiponectin acts in the body. In each of these ways it undergoes a conformational change and carry out its role. The mechanism by which it undergoes such structural change and subsequent physiological following structural change is not clearly defined. In muscle tissue they promote beta-oxidation of fatty acids and in liver they cause inhibition of gluconeogenesis and promote glycogenesis.

With raising incidence of obesity in the industrial world, various ways and tests by which we can detect the risk obesity in early stage itself and other comorbidities are also on the rise.

Based on various studies and researches it has now been understood that adipocytes are not just a mass of fat stores, but it is an endocrine organ secreting various hormones. Individual hormones which are secreted by adipose tissues and their functions are not completely studied.

The state of chronic inflammation typical of obesity occurs at metabolically relevant site such as liver, muscle and adipose tissue. Increased inflammatory marker IL – 6, associated with obesity might interfere with insulin action by suppressing insulin signal transduction which, in turn interferes with anti – inflammatory effects of insulin.

Leptin, an adipocyte specific protein is elevated in obese, has proaggregatory effect on platelets and also elicit inflammatory responses. Hence obesity is considered to be a pro inflammatory state and inflammatory markers like CRP and TNF are elevated in isolated obese individuals.

Studies supporting obesity as a major determinant of CRP in metabolic Syndrome

Steven and zinnman (ADOPT Trial), was conducted in 1999 in view of determining the microvascular and macro vascular complications and related comorbidities in association with obesity or hypertension. They have also found that metabolic syndrome is more prevalent in recently diagnosed diabetics even if there is no confounding factors. It is commonly seen in relation with very high inflammatory activity and defect in clot retraction pathways.

The metabolic syndrome is most common with type 2 diabetes, and cerebrovascular accidents are more common in individuals with metabolic syndrome than subjects with type 2 diabetes who do not have the metabolic syndrome. Furthermore, higher levels of c reactive protein, fibrinogen and PAI-1 in non-diabetic subjects has been associated with metabolic syndrome.[77]

Obesity plays an important role in mediating these effects, and insulin resistance has an added effect.

William et al 78 analyzed the association between C Reactive Protein, obesity and the metabolic cardiovascular risk factors. The authors demonstrated an association between CRP and BMI, in young men and women, independent of the other cardiovascular risk factors. As this study was conducted only in a

group of women and men aged 26 years and did not use a high sensitivity assay for C Reactive protein measurements, leads to a potential underestimation of differences among study groups with low CRP concentrations.

Clinical research article published in Circulation 2004 and supported by American Heart Association concludes, that CRP was strongly related to all anthropometric and direct measures of total and central abdominal obesity. 80, 81

Margit Froehlich, Armin Imhof et al found an association between the acute-phase marker CRP and a number of disorders characterizing the metabolic syndrome. They concluded that the metabolic syndrome is associated with a systemic inflammatory response, which pays an important pathogenic role in atherothrombotic disease. 82

Christine and. Mukkammal carried out a study on obesity in the year 2007 to march 2009, in which they proposed that increased BMI in spite of variations in race, nationality and community including both males and females were found to have elevated level of CRP in serum. The p-value of the results were adjusted for age groups, lifestyle practices and nationality/ racial variation , sex , even after the changes which were made in measurement CRP values were found to be persistently elevated.

According to Madric84 study, CRP levels are significantly elevated in patients with metabolic syndrome and NCEP protocol and C-Reactive concentrations in serum correlates significantly with central obesity.

A study conducted by some researchers in Japan proposed in both male and female sex level of C-Reactive Protein correlates significantly with syndrome X. In the same study they concluded that rise in C-Reactive Protein was significant more in females that too non-smokers who are already having the predisposing factors of metabolic syndrome.

Ridker, Buring et al 86 have observed that measurement of CRP adds clinically important prognostic information to the metabolic syndrome.

Studies not supporting obesity as a major determinant of CRP in metabolic Syndrome

Tracey McLaughlin, FahimAbbasi, et al 87 (Circulation 2006) observe that CRP concentrations are elevated predominantly in obese individuals who are also insulin resistant and fall is parallel with weight loss – associated improvements in insulin resistance. The relation between CRP concentrations and insulin resistance is independent of obesity.

MATERIALS AND METHODS

Materials and Methods

The study was conducted in Thanjavur Medical College Hospital, Thanjavur, and Tamilnadu. The study was conducted in the Department of Internal Medicine. The study period extended between June 2007 and October 2008. It was a carefully selected study population of metabolic syndrome. National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria was used to define metabolic syndrome in the study group.

The patients were selected on the basis of inclusion and exclusion criteria. In all those patients, high sensitivity C-reactive protein was estimated and analyzed. The study included both sexes. Fifty patients were included in the study group after applying exclusion criteria. The sample population was predominantly obtained from the patients attending the diabetic and hypertension clinic and medicine outpatient department of our hospital.

This is a cross sectional population based study. The study population was selected randomly among the out patients. Out of the many definitions applied worldwide for metabolic syndrome, the ATP III guidelines is the only which has been approved and accepted by many quarters. It is the one which has been extensively used in the clinical trials of metabolic syndrome too.

Hence, we applied the NCEP/ATP guidelines (with current modification) for selecting the study group.

Definition of terms

Obesity was defined as a BMI $\geq$ 30kg/m^2 (WHO 2000)

Metabolic syndrome – presence of at least three components among the major five parameters in the criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III

1. Central obesity (waist circumference > 88cm in women and > 102cm in men).
2. Low serum HDL cholesterol (<50mg/dL in women and < 40 mg/dL in men) or on specific medication,
3. High serum triglyceride ($\geq$ 150 mg/dL) or on specific medication,
4. Elevated blood pressure ($\geq$130 mmHg systolic / $\geq$ 85 mmHg diastolic) or on specific medication,
5. Abnormal glucose homeostasis (fasting plasma glucose $\geq$ 100 mg/dL) or on specific medication or previously diagnosed type 2 diabetes.

Inclusion criteria

The patient should fit into the definition of metabolic syndrome as defined by ATP III guidelines, as given above.

Exclusion criteria

Past history of coronary artery disease

Past history of cerebrovascular accidents

Patients with

1. Active infection
2. Inflammation
3. Neoplasm
4. Autoimmune / Collagen vascular disease
5. Pregnancy
6. Terminal illness
7. Smokers
8. Renal and hepatic dysfunction

Were excluded from the study.

A proforma was drafted including the details about the patient and specifically related to known risk factors and factors that can elevate hs – CRP.

Physical examination

The patients underwent routine physical examination and anthropometric measurements.

Waist Circumference and Weight & Height calculation:

In patients wearing very loose clothing, without any footwear and measured weight was rounded off to multiples of 100 grams.

Measurement of height was done by using WHO proposed protocol with making the patients stand without any footwear. This method is the commonly followed one all over the world.

Body mass index (BMI) was calculated by body weight in kilogram divided by square of height in meters.

Waist circumference – it is measured at midpoint between lower costal margin and highest point of iliac bone in mainly around the widened region of gluteus using a measurement tape which is circled over the abdomen without any wrinkles and stretching. While measuring there should not be any pressure on the surface of body. Values are rounded off to nearest 1 mm. Quality of the tape is to be in such way that it should not be too elastic and too rigid.

Assessment of biomarkers

Levels of fasting glucose, HDL-C, and triglycerides were determined by enzymatic methods using an auto analyzer, whereas hs-CRP levels were measured by latex-enhanced nephelometry (Fully Automated Nephelometry BN 100).

Estimation

The sample was withdrawn after a period of overnight fasting. 5ml of venous blood was collected in a sterile glass tube. The blood was allowed to clot centrifuged and analyzed for high sensitivity CRP levels using NEPHELOMETRY method. A value of > 0.3mg/dL was taken as a positive hs-CRP in our clinical study.

Nephelometry

It is a method which measures the amount of photon energy which were scattered by the particulate matter using a sensor rather than measuring the photon energy in straight line with the light source. Most of the instruments measures the energy usually at 90 degrees to light source, while some others Measures at angles lesser than 90 degrees.

There are lot of ways in which protein level can be estimated. Among them most important one is Nephelometry. It is useful in assaying various proteins such lipoproteins, CRP, RA factor, ASO titer, various components of complement system. Other methods which are useful are Turbidometry, Biuret method.

Lowest range at which turbidimetry can detect and protein level is around 30 microgram/milliliter. But Nephelometry can detect and assay protein even up to 10 microgram/milliliter. Thus nephelometry is method of choice in

detecting and assaying proteins when there is a need for monitoring even minor variation in their serum level.

RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

The study sample included fifty patients, male and female. The age of the study sample ranged from 30yrs to 77yrs.

Incidence

Age in years	30-39	40-49	50-59	60-69	>70	
No of Cases	3(6%)	14(28%)	19(38%)	10(20%)	4(8%)	

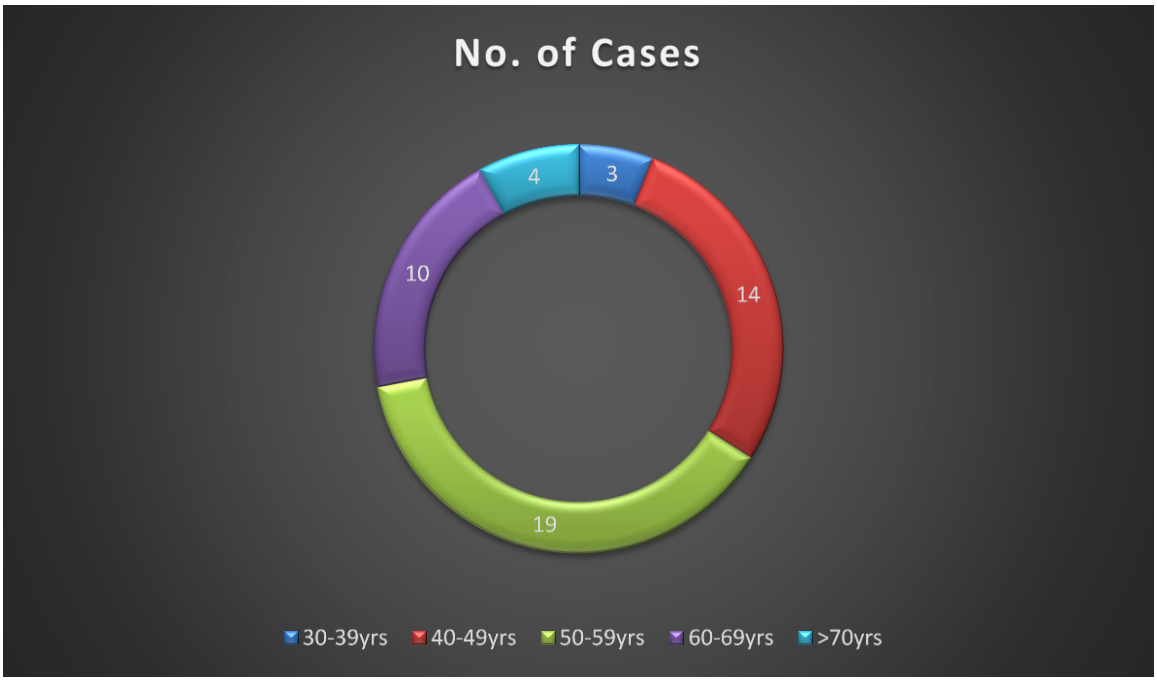


Figure 1

The study sample included 18 males and 32 females

SEX	NO. OF CASES	PERCENTAGE
MALES	18	36%
FEMALES	32	64%

AGE BASED CLASSIFICATION OF PATIENTS

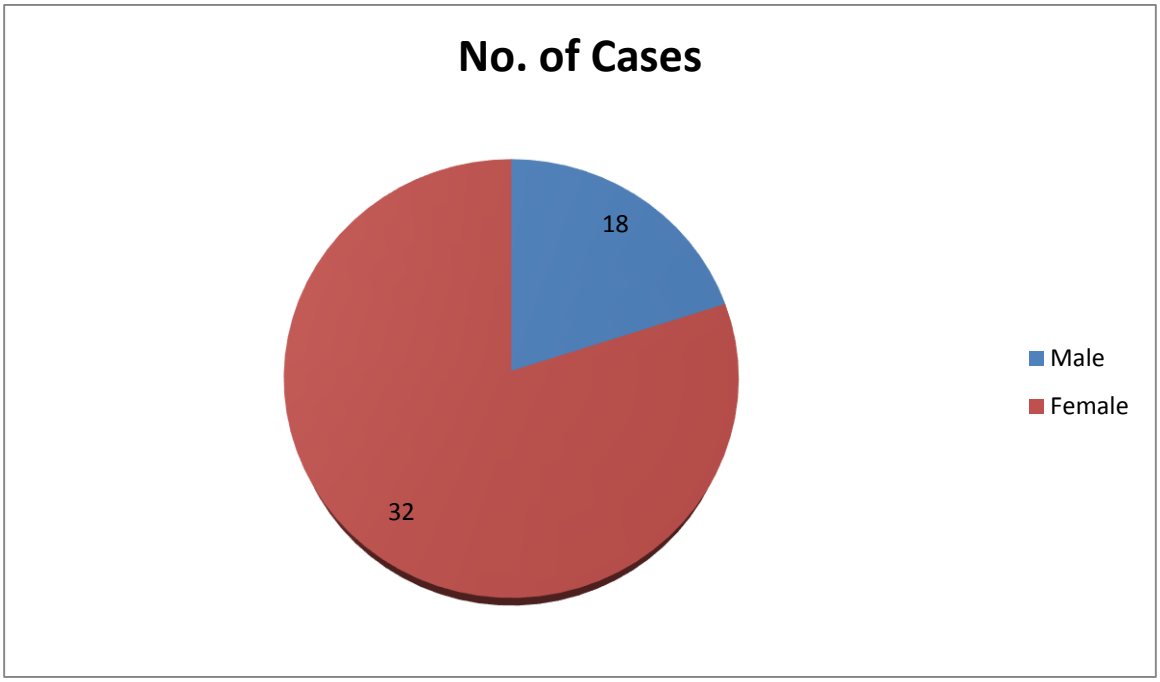


Figure 2

The high sensitivity CRP levels are classified according to cardiovascular risk status as

<0.1	mg/dL	low risk
0.1-0.3	mg/dL	average risk
>0.3	mg/dL	high risk

Hs – CRP levels mg/dL	**No. of Males**	**No. of Females**
<0.1	0	0
0.1-0.3	(12%)	8(16%)
>0.3	3(6%)	32(64%)

Most of the research projects takes the hs-CRP levels of > 0.3 mg/dL as a positive result. In this study too, we have taken any value above 0.3 mg/dL as positive level. Hence, out of the sample group of 50 patients 42 (84%) showed an increase in hs-CRP levels and 8 (16%) showed levels <0.3 mg/dL. Out of the 42, 29 were females and 13 were males.

	No. of Males	**No. of Females**
Positive hs-CRP (>0.3 mg/dL)	13 (26%)	29 (58%)
Negative (<0.3 mg/dL)	5(10%)	3(6%)

HS-CRP RELATION WITH SEX

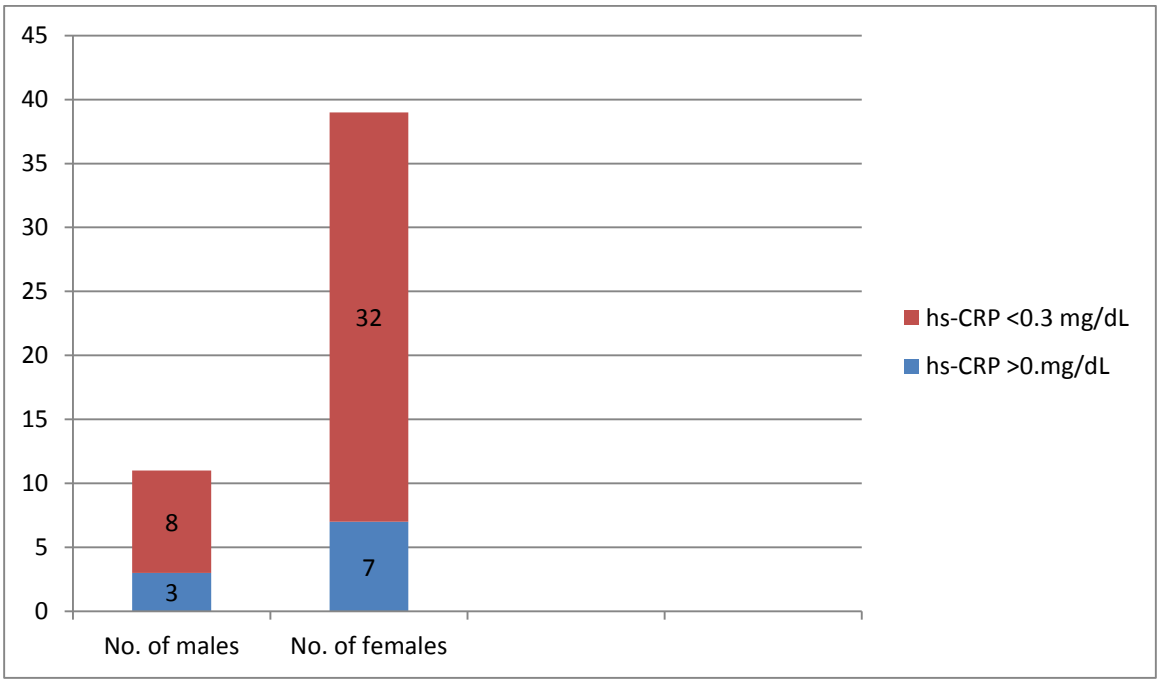


Figure 3

The association between hs- CRP levels and individual components of metabolic syndrome was analyzed.

The study sample of 50, included 41 subjects with increased waist circumference (>90 cm in males and > 80cm in females). Out of the 41, 39 had hs – CRP levels of > 0.3 mg/dL, whereas only 3 of the remaining 11 with waist circumference (<90 cm in males and < 80cm in females) had levels of > 0.3 mg/dL.

	Increased Waist Circumference 41 (82%)	Normal waist circumference 9 (18%)
hs-CRP> 3.0 mg/dL	39	3
hs-CRP <0.3 mg/dL	2	6

HS-CRP IN RELATION WITH CENTRAL OBESITY

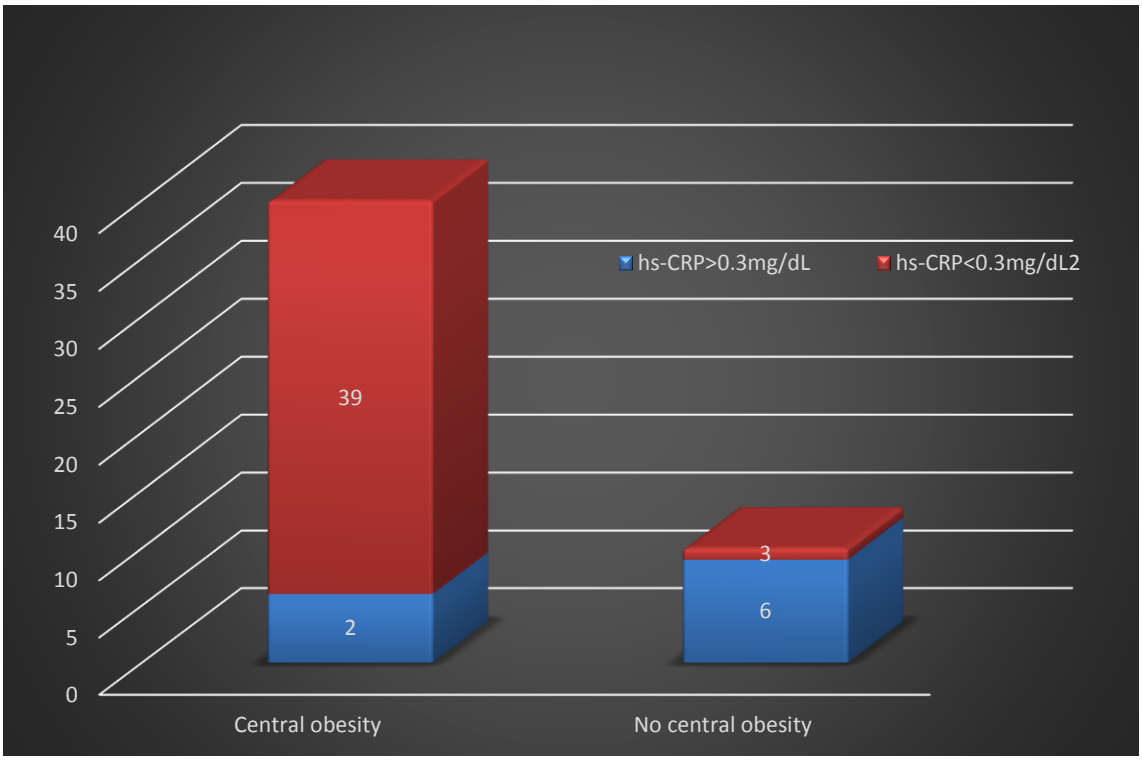


Figure 4

The study sample of 50, included 38 subjects with low HDL levels. (<40 mg/dL in males and < 50mg/dL in females). Out of the 38, 32 had hs – CRP levels of > 0.3 mg/dL and 6 of the 19 with high HDL levels > 0.3mg/dL.

	Low Plasma HDL 38 (76%)	High Plasma HDL 12 (24%)
hs- CRP> 0.3mg/dL	32	10
hs- CRP < 0.3 mg/dL	6	2

HS-CRP IN RELATION WITH HDL

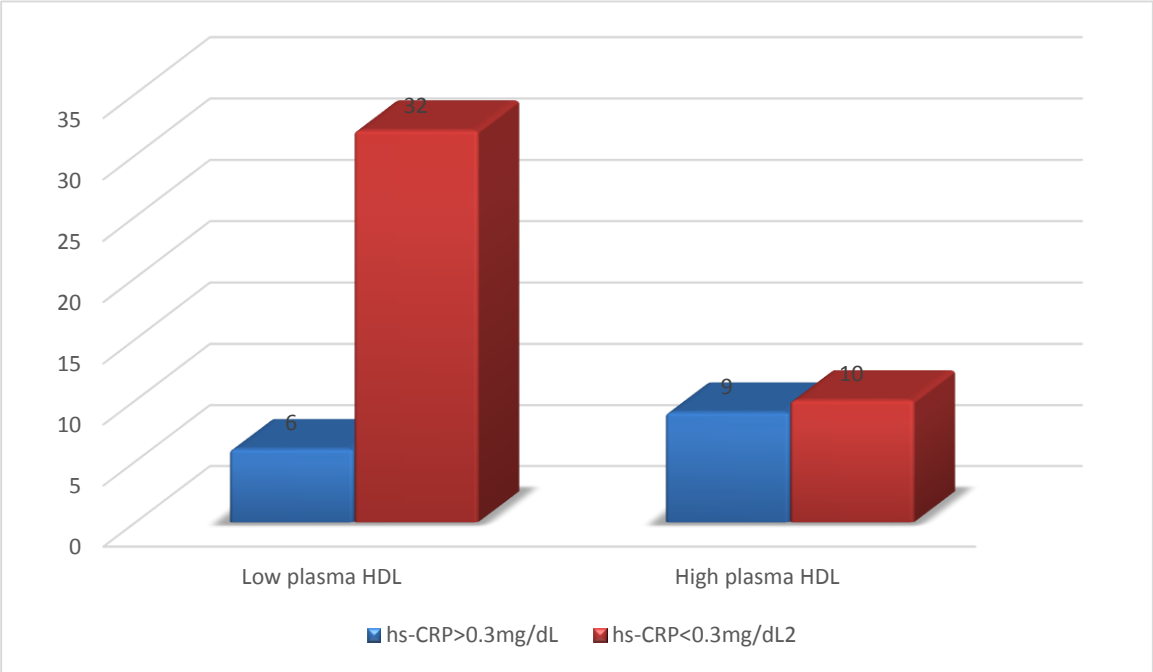


Figure 5

The study sample of 50, included 28 subjects with triglyceride levels of ≥ 150 mg/dL and 22 had levels lesser than it. Out of the 28, only 20 had hs – CRP levels of > 0.3mg/dL; whereas all 22 of the 22 with lower triglyceride levels had levels of >0.3 mg/dL.

	Serum TGL ≥ 150mg/dL 28 (56%)	Serum TGL < 150mg/dL 22 (44%)
hs-CRP > 0.2 mg/dL	20	22
hs-CRP < 0.3mg/dL	8	0

HS-CRP IN RELATION WITH TGL

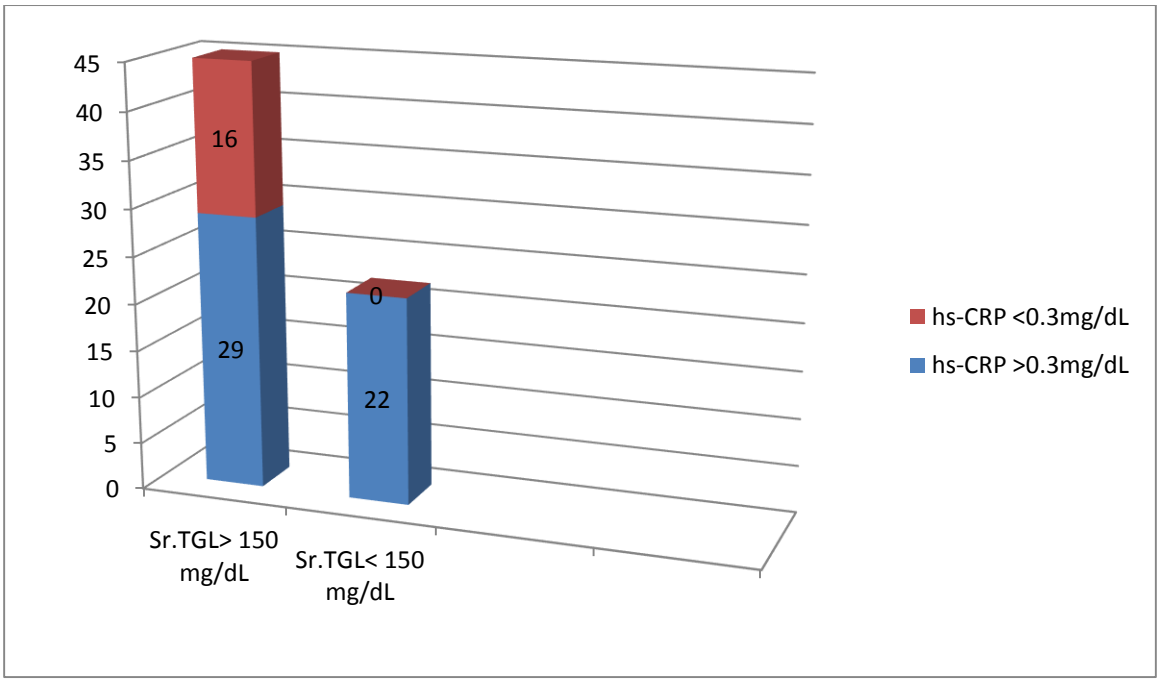


Figure 6

Our study sample of 50, included 41 subjects with blood pressure > 130/85 mmHg. Out of the 41, hs- CRP levels were above 0.3mg/dL in 34 subjects. In the non-hypertensive group of 9, hs-CRP was elevated in 8 subjects.

	Hypertensive 41 (82%)	Non – hypertensive 9 (18%)
hs-CRP > 0.3mg/dL	34	8
hs-CRP < 0.3mg/dL	7	1

HS-CRP IN RELATION WITH HYPERTENSION

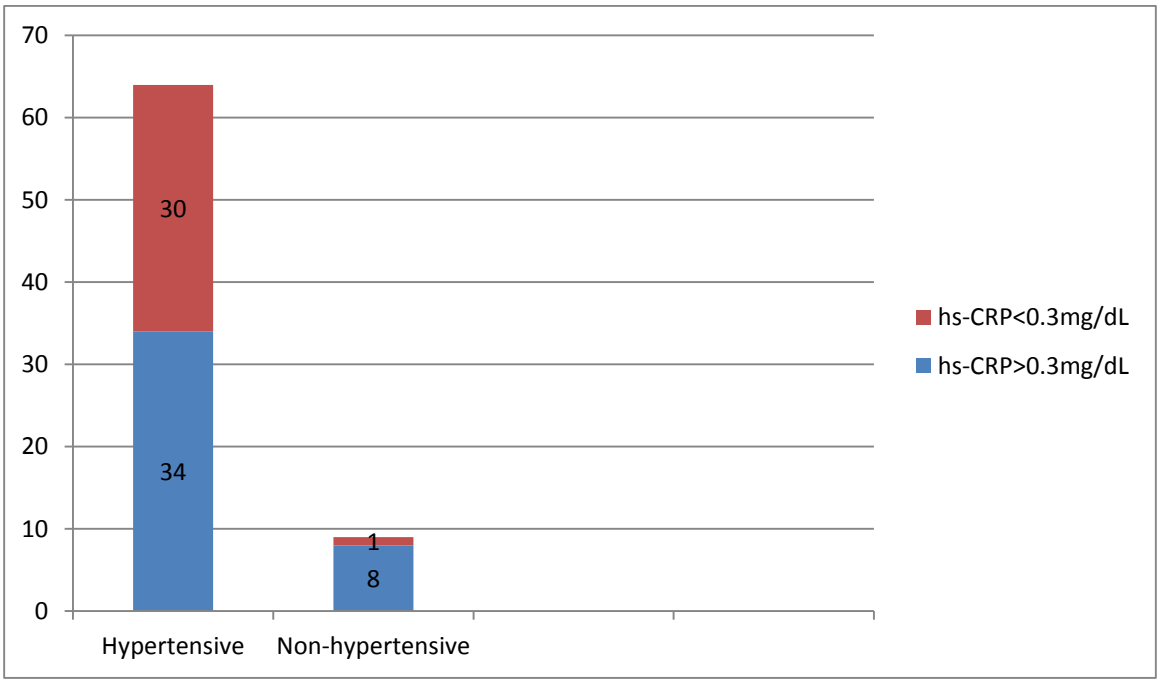


Figure 7

The current guideline used for fasting blood sugar was > 100mg/dL instead of the previous level of > 110mg/dL. We employed the current guideline in defining raised blood sugar levels in the sample group. Out of the 50 members of the study group 40 had impaired fasting glucose or known diabetic and 10 had normal glucose. In the group of 40, 34 had an elevated hs-CRP and among the 10, 5 had an elevated hs-CRP.

	Impaired fasting glucose 40 (80%)	Normal 7 (14%)
hs-CRP > 0.3 mg/dL	34	5
hs-CRP < 0.3 mg/dL	6	5

HS-CRP IN RELATION WITH IMPAIRED GLUCOSE TOLERANCE

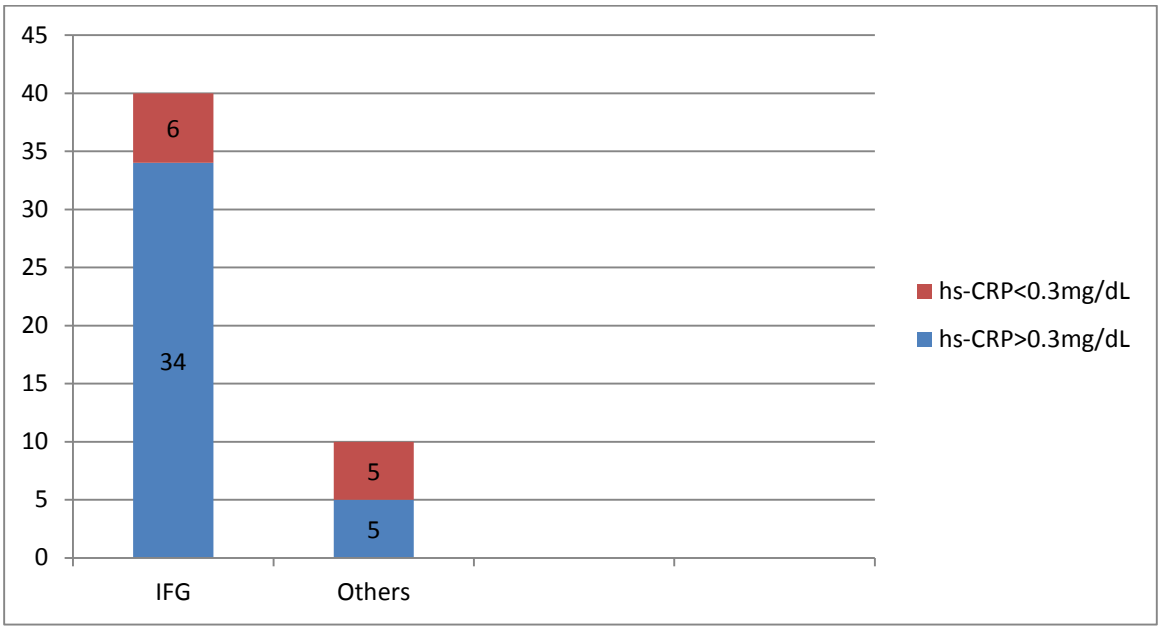


Figure 8

The study sample of 50, included 41 subjects with BMI $\geq$ 30kg/m^2. Out of the 41, 33 subjects had hs-CRP levels > 0.3mg/dL. Of the remaining 9, 2 subjects had elevated levels of hs-CRP.

	BMI $\geq$ 30 Kg/m^2	BMI < 30 Kg/m^2 9
	41(82%)	(18%)

hs- CRP > 0.3mg/dL	33	2
hs- CRP < 0.3 mg/dL	8	7

HS-CRP IN RELATION WITH BMI

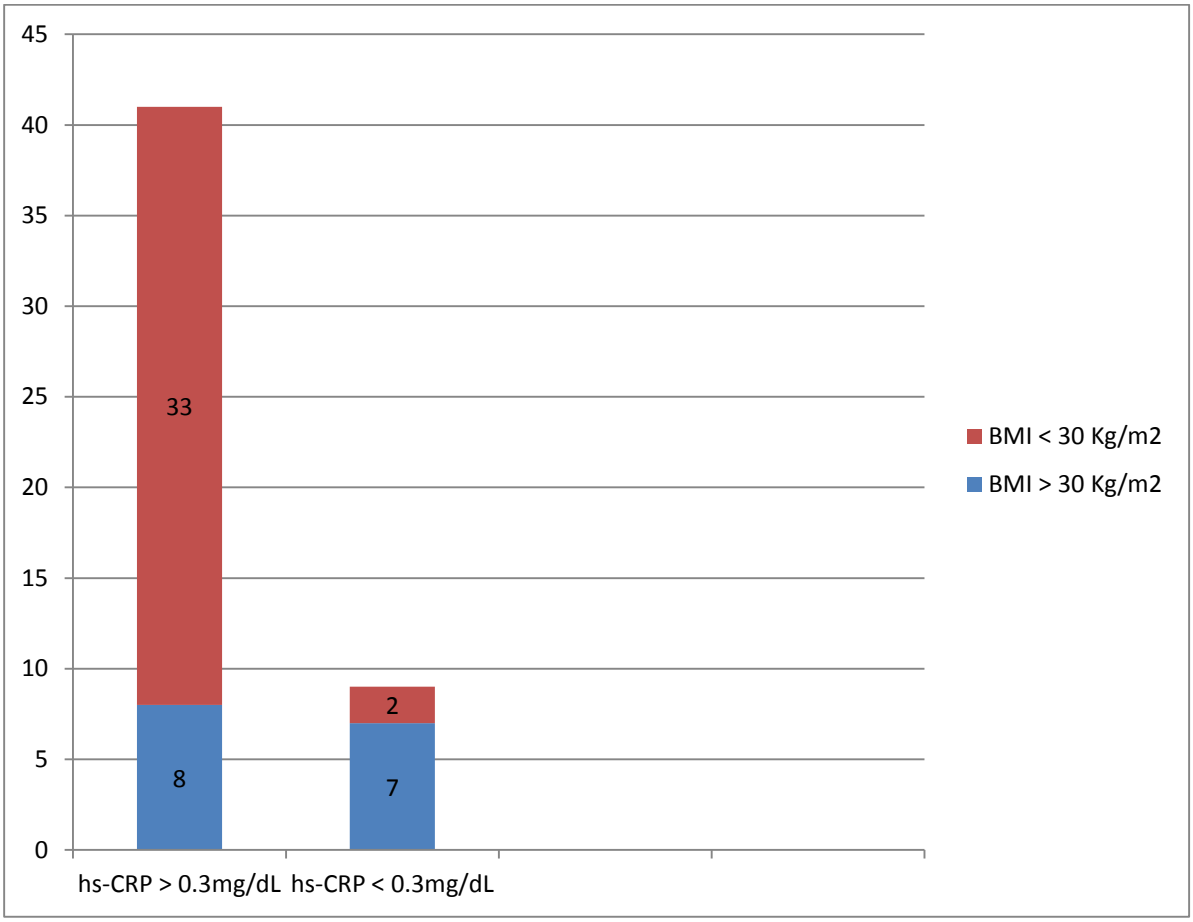


Figure 9

Analysis of results

The results were analyzed with confidence interval testing and using chi – square test.

a) The levels of high sensitivity CRP are higher in metabolic syndrome. Using the confidence interval method, 42 of the 50 have high hs- CRP levels and it falls outside the confidence interval of 0.95. Hence the study result is consistent with the claim that hs- CRP levels are high in metabolic syndrome.

b) In this study population of 18 male and 32 female, 13 male and 29 females showed increase in hs – CRP levels.

Using the chi – square hypothesis, the null hypothesis that there is no difference in hs – CRP levels between two sexes is disproved in this study. In this there is a definite evidence ($p < .002$) that females with metabolic syndrome has high hs – CRP when compared to males.

c) The study sample of 50, included 41 subjects with central obesity (waist circumference > 90cm in males and > 80 cm in females). Out of the 41, 39 had hs – CRP levels of > 0.3 mg/dL, whereas only 3 of the remaining 9 with normal waist circumference had levels of > 0.3 mg/dL.

Using chi – square test, a p value of <0.001 (strongly significant) was derived. This is a telltale evidence that out of all the components of metabolic syndrome, hs – CRP levels depend on waist circumference significantly. Hence, obesity is an independent inflammatory state on itself.

d) The study sample of 50, included 38 subjects with low HDL levels. (< 40mg /dL in males and < 50 mg /dL in females). Out of the 38, 32 had hs – CRP levels of > 0.3 mg/dL and 10 of the 12 with high HDL levels had levels of > 0.3mg/dL.

Using chi –square test, a p value of 0.336 (insignificant) was derived. Hence, changes in plasma HDL levels do not affect the levels of hs – CRP in metabolic syndrome.

e) The study sample of 50, included 28 subjects with triglyceride levels of $\geq$ 150 mg/dL and 22 had levels lesser than it. Out of the 28, only 20 had hs – CRP levels of > 0.3mg dL; whereas 22 of the 22 with lower triglyceride levels had levels of >0.3mg/dL.

Using chi – square test, a p value of 0.696 (insignificant) was derived. This means that elevation of hs – CRP levels in metabolic syndrome is independent of plasma triglyceride levels.

f) In this study sample of 50, 41 were hypertensive. Out of the 41, hs – CRP levels were above 0.3mg/dL in 34 subjects. In the non – hypertensive group of 9, hs – CRP was elevated in 8 subjects.

Using chi – square test, a p value of 0.614 (insignificant) was derived. This means that elevation of hs – CRP levels in metabolic syndrome is independent of hypertension.

g) Out of the 50 members of the study group 40 had abnormal glucose homeostasis (impaired fasting glucose) and 10 were normal. In the group of 40 subjects, 34 had an elevated hs – CRP and among the 10 normal subjects, 5 had an elevated hs – CRP.

Using chi – square test, a p value of 0.128 (moderate significance) was derived. This means that elevation of hs – CRP levels in metabolic syndrome is moderately dependent of glucose status.

DISCUSSION

Discussion

Analysis of hs – CRP levels in patients with metabolic syndrome.

Inference 1

This study shows statistical evidence that hs – CRP levels are elevated in metabolic syndrome.

The above inference is supported by the studies of

Margit Frohlich, Armin Imhof et al[82]

MADRIC[84] study – CRP levels are significantly elevated in patients with metabolic syndrome

Ridker, Buring et al[86].

Inference 2

In our study, hs - CRP levels in women with metabolic syndrome is significantly higher when compared to levels in men with metabolic syndrome.

Though there are not many studies approving or disproving this result, the following studies support it.

Study by **Noriyuki Nakanishi, Tsunehito Shiraishi, Mariko Wada et al**, [and 85] states that an increase in CRP concentration is more pronounced in women.

Martin K. Rutter, James B. Meigs, et al[88] have stated that elevated CRP levels are related to insulin resistance and the presence of the metabolic syndrome, especially in women.

Inference 3

Levels of hs – CRP are strongly associated with changes in waist circumference and the p value derived was < 0.001, an indication of its strong association. This inference is supported by many other studies which support obesity as an independently inflammatory state.

According to **MADRIC**[84] study, metabolic syndrome and all its individual components were associated with high CRP levels, with the strongest association being found for high waist circumference (P <0.001).

Clinical research article published in **Circulation 2004** and supported by American Heart Association concludes that CRP was strongly related to all anthropometric and direct measures of total and central abdominal obesity.

Inference 4

Levels of hs – CRP are independent of plasma HDL levels in metabolic syndrome. In this study, there is no statistical significance between the levels of plasma HDL and hs – CRP.

This inference is supported by,
Margit Frohlich, Armin Imhof, et al[82] and
MADRIC[84] study

Inference 5

Levels of hs – CRP is independent of Plasma triglycerimia levels. This is one inference in our study which does not correlate with the results of other studies.

Margit Frohlich, Armin Imhof, et al[82] in a population based study has concluded that there is a statistically significant correlation between plasma TGL levels and hs – CRP levels.

In our study 12 values of plasma TGL lies between 140-150 mg/dL which could have contributed to the discrepancy in the results when compared to other studies. This needs to be studied further.

Inference 6

Levels of hs – CRP in metabolic syndrome does not depend on the hypertensive status of an individual. This statement derived from our study is supported by,

Steven E, Kahn, Bernard Zinman et al.,[76] ADOPT, A Diabetes Outcome Progression Trial – where even in non-diabetic subjects the metabolic

syndrome has been associated with higher levels of CRP as well as PAI – 1 and fibrinogen.77

Inference 7

Levels of hs – CRP does have a moderately significant association with diabetic status of the individual. In our study there is moderate statistical significance (p -0.126) between the diabetic status and hs – CRP. This statement derived from our study is supported by,

Tracey and Fahim et al.,study where they suggested insulin resistance is significantly associated with elevated levels of CRP independent of obesity.

Steven E, Kahn, Bernard Zinman et al.,[76] ADOPT, A Diabetes Outcome Progression Trial – where even in non-diabetic subjects the metabolic syndrome has been associated with higher levels of CRP as well as PAI – 1 and fibrinogen.77

Inference 8

Levels of hs – CRP does have a significant association with Body Mass Index. In our study there is statistical significance (p <0.001) between the BMI and hs – CRP.

This inference is supported by,

Margit Frohlich, Armin Imhof, et al[82].

CONCLUSION

Conclusion

1. The levels of serum hs – CRP are elevated in metabolic syndrome.
2. The levels of hs – CRP are significantly elevated in obese individuals.
3. Obesity is a pro – inflammatory state all by itself.
4. Levels of hs – CRP are significantly elevated in patients with central obesity.
5. Levels of hs – CRP is slightly dependent of blood glucose in patients with metabolic syndrome.
6. Levels of hs – CRP is higher in women metabolic syndrome than men with metabolic syndrome.
7. Levels of hs – CRP is independent of plasma triglyceride levels in patients with metabolic syndrome.
8. Plasma HDL levels will not affect the levels of hs – CRP in metabolic syndrome.
9. Levels of hs – CRP is independent of hypertensive status in patients with metabolic syndrome.
10. Our study results are comparable with other Indian and foreign study results.

FUTURE

Patients with metabolic syndrome have higher levels of hs – CRP than those without this syndrome. Patients with elevated hs – CRP levels of > 0.3mg/dL are considered to be at a higher risk for the development of cardiovascular events than others.

According to Framingham score this hs – CRP level is associated with a ten year risk of coronary heart disease of 10-20%. Risk stratification by hs – CRP gives prognostic information in patients with metabolic syndrome.

Patients with metabolic syndrome and elevated hs – CRP values should be subjected to an appropriate life style modification at an early age, treatment with low dose aspirin, lipid lowering medications, non-pharmacological modifications and global education. This study opens up new avenues for further research in the topic of the ever changing field of metabolic syndrome.

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PROFORMA

Name	Age			Sex	
Occupation			OP NO		
Address					
Diagnosis					
Presenting complaints					
Past history	HT		DM	Malignancy	
	CVA		CAD	Renal disease	
	Autoimmune		Hyperlipidemia		
	Collagen vascular Disease				
Personal history	Smoker		Alcohol		
Physical examination	BP	Systolic mmHg			
		Diastolic mmHg			
	PR-				
	Height(cm)	Weight(kg)	BMI Kg/m^2		
	Waist circumference cms		Hip circumference cms		
	Waist/hip ratio				
Investigations					
Hb gm%	TC	DC	RBC	PCV	ESR
Urine	Albumin	Sugar		Deposits	
Fasting blood sugar mg/dL					
Blood urea mg/dL			Sr. Creatinine mg/dL		
ECG			LFT		
Sr. TGL mg/dL	Sr. HDL mg/DL		USG Abdomen		
hs- C reactive protein mg/dL			CT abdomen		

ABBREVIATIONS

MS	-	Metabolic Syndrome
ATP-III	-	Adult Treatment Panel III
IDF	-	International Diabetic Federation
hsCRP	-	High sensitive C-reactive Protein
NHANES III	-	National Health and Nutrition Examination Survey
EGIR	-	European Group for study of Insulin Resistance
HDLC	-	High Density Lipoprotein Cholesterol
LDL	-	Low Density Lipoprotein
TGL	-	Triglycerides
BMI	-	Body Mass Index
WHO	-	World Health Organization
JAK/STAT	-	Janus Kinase
ACTH	-	Adrenocorticotropic Hormone
POMC	-	Proopiomelanocotin

Alpha-MSH	-	Alpha Melanocyte Secreting Hormone
TNF-alpha	-	Tumour Necrosis Factor Alpha
CVD	-	cerebrovascular disease
CAD	-	Coronary Artery Disease
PVD	-	Peripheral Vascular Disease
NASH	-	Non-Alcoholic SteatoHepatitis
MI	-	Myocardial Infarction
ADOPT	-	A Diabetes Outcome Progression Trial
FCRS	-	Framingham Coronary Heart Disease Risk Score
NCEP	-	National Cholesterol Education Program

	NAME	Age/Sex	Waist Circumference	BP	FBS	Sr.HDL mg/dl	Sr.TGL	hs-CRP
1	FATHIMA	50/F	80	140/90	142	52	195	0.57
2	MEENA	55/F	124	150/100	178	34	220	1.1
3	AROCKIA SAMY	77/M	104	140/100	126	41	135	0.63
4	BALAGURU	45/M	108	160/110	163	40	118	0.51
5	BARATHI	62/F	118	120/80	192	39	170	1
6	BANUSHANKAR	45/M	127	140/90	118	44	95	2.1
7	BASKARI	42/F	110	150/90	126	58	210	0.45
8	GUNASEKARAN	49/M	90	170/110	178	35	140	1.3
9	JAMIMA	30/F	86	150/100	95	31	210	0.11
10	JEYAKUMAR	60/M	110	140/90	130	40	125	1.78
11	JEYALAXMI	55/F	120	130/90	140	56	110	1.3
12	JOSEPHINE	59/F	88	160/90	122	33	170	0.99
13	KALYANI	60/F	109	180/110	147	29	220	1.3
14	KARUNA	40/F	100	150/90	154	43	165	0.89
15	MANI	60/M	117	150/110	126	47	90	1.65
16	MANGALAM	45/F	77	120/80	138	32	210	0.24
17	MANICKAM	73/M	87	140/90	87	36	245	0.17
18	NAGARAJAN	62/M	122	160/110	118	42	150	2.12
19	NARAYANI	43/F	98	130/80	92	45	165	1.11
20	NOORAHMED	45/M	108	150/100	158	41	115	1.3
21	PADMAVATHI	53/F	100	140/110	195	37	155	1

22	PANDIAMMAL	50/F	92	110/80	232	42	135	0.55
23	PONMANI	48/F	118	110/70	86	45	180	1.32
24	POUNAMBAL	40/F	114	150/100	190	45	155	0.46
25	PREM	63/M	88	150/100	82	31	205	0.11
26	SOBIN	63/M	92	130/80	212	30	145	1.72
27	RANI	55/F	129	170/90	80	41	120	2.15
28	MANOJ	50/M	121	160/90	260	35	160	3
29	SAMIPILLAI	50/F	109	180/100	124	37	105	0.55
30	SAROJA	60/F	99	160/90	95	39	205	1.53
31	SAROJA	45/F	113	130/70	148	40	95	0.58
32	SEEMA	39/F	74	150/100	166	32	130	0.79
33	SELVAM	49/M	102	160/90	129	39	115	1.5
34	SELVARANI	70/F	81	160/100	189	33	135	1.65
35	SHANTHI	52/F	78	150/100	84	37	170	0.19
36	SUBRATHA	39/F	114	110/70	114	35	155	0.57
37	SUSAI MARY	60/F	118	140/100	173	34	200	0.99
38	SURESH	55/M	85	160/120	250	32	195	0.21
39	THARA	43/F	120	100/60	155	41	175	1.22
40	THANGAMANI	52/F	96	140/80	131	29	85	0.68
41	MANOHARI	55/F	119	140/110	166	33	100	0.74
42	LALITHA	50/F	104	160/90	82	44	110	0.85
43	VASANTHA PRIYA	56/F	89	160/100	118	39	155	0.71
44	VASANTHA	56/F	123	130/80	172	38	165	0.51
45	VEERALAXMI	51/F	106	120/80	132	43	150	1.36
46	KRISHNAMMAL	55/F	120	140/100	127	32	95	1.54
47	VELLAISAMY	77/M	124	150/90	148	37	210	1.33
48	RAJAVEL	52/M	102	150/100	130	36	170	0.78
49	VIJAY	48/M	94	160/110	93	48	190	0.25
50	SUGUMAR	60/M	83	150/100	130	43	165	0.28

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .R.THILAKH BABU,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant